

REMARKS

Claims 1-9, 13, 16, 19-21, 23, 24, 26-28, 30-34 and 42-47 stand rejected on various grounds. Of these, claims 16 and 43 have been canceled (the limitations of claim 43 have been added to the claim from which it depends), and all pending independent claims (1, 30 and 42) have been amended. Claim 9 has also been amended to cover a preferred method wherein the PET indicative of the protein present in the sample comprises a splice junction. Basis for this new language appears at page 35, line 6. Basis for the amendments to the independent claims appears in the claims as originally submitted, as well as at page 5, line 30, page 27 line 1, page 34 line 1, page 35, line 6, page 98, line 28, in Example 8, and particularly in text starting at page 159 *et seq.* Upon entry of this paper, claims 1-9, 13, 19-21, 23-24, 26-28, 30-34, 42, and 44-47 will be pending and under consideration.

Applicants submit that, in view of the amendments to the claims and the arguments herein, the cited references, either individually or in combination, clearly fail to disclose or suggest the subject matter of the invention as now claimed, taken as a whole. Accordingly, Applicants respectfully traverse the rejections to the extent they are applied to the claims as amended.

All claims have been amended to be limited to clearly patentable subject matter and to respond to the Examiner's helpful efforts at clarification of the claim language. No new issues have been introduced. No claims have been added. All claims are in condition for allowance.

35 U.S.C. § 112, Second Paragraph Rejections

Claims 1 and 2 were rejected under 35 U.S.C. § 112, Second Paragraph, based on alleged indefiniteness of the phrase "selectively interact." This phrase is intended to have its ordinary meaning, i.e., to act upon one in preference to another or others. It is well understood by the artisan, and is intended to leave open the possibility that there may be some cross reactivity, as is ubiquitous in biology.

Rejected claim 16 has been canceled.

Rejected claims 30 and 42 (as well as amended claim 1) have been amended to make explicit what is meant by “splice variant proteins,” namely, as is well understood in the art, and as the examiner correctly perceived, proteins that are the expression products of RNAs alternatively spliced from a single DNA. Applicants thank the Examiner for pointing out this potential ambiguity. This amendment is submitted to overcome the rejection.

35 U.S.C. § 102 Rejections

All claims as amended are now limited to methods and apparatus for detection of multiple proteins at least one or more of which is a “splice variant protein” as defined above and in the claims. Applicants submit that the Katz 102(e) reference does not mention splice variants, and accordingly the outstanding 102 rejection is obviated. Furthermore, all claims as amended require the step of using a secondary capture agent. As the Examiner has indicated, Katz fails to disclose such use (Office Action - Paragraph 11).

35 U.S.C. § 103 Rejection

Neither of the secondary references disclose that it is possible or desirable to detect splice variant proteins, and accordingly, the obviousness rejections have been obviated and cannot fairly be applied to the claims as amended.

The Suzuki reference discloses a panel of antibodies for determining the presence of 40 amino acid and 42 amino acid beta amyloid proteins, *not peptides produced by digestion* as required by all claims herein. Furthermore, *these are not splice variants* (see, e.g., http://www.upstate.com/features/app_lp.asp -- Amyloid Precursor Protein (APP) and Amyloid β ($A\beta$)). Rather, multiple APP isoforms, generated by alternative splicing, have been described with a 770 amino acid isoform being the largest and a 695 amino acid isoform being most prevalent in neuronal cells. Sequential *proteolytic processing* of the 695 amino acid isoform of APP give rise to the $A\beta$ peptides, known as $A\beta$ x-40, x-42 and x-43 for the number of amino acids they contain. While they are produced by the cleavage of one of the 10 or so different splice variants, they *are not themselves splice variants*. Thus, rather than being expressed from

different RNAs spliced from the same DNA, a larger protein expressed from a single RNA is differentially cleaved at its C-terminus to produce either the 40 AA or the 42 AA form.

The referred-to passage in Wagner (col. 2, line 14 *et seq.*), asserted as a basis to reject claims 7-9, at best teaches the use of “cellular extract,” or its digested products; the use of “solubilized” membrane proteins; and the use of “fragments of the expression products of a cell.” There is no teaching or suggestion in this passage that the protein should be denatured, as required by all presented claims. In fact, Applicants have been unable to find in the Wagner specification a teaching or suggestion of the use of denaturation and proteolysis for sample preparation. Furthermore, Applicants have been unable to find in Wagner *any mention whatsoever* of splice variant proteins.

CONCLUSION

In view of the above amendments and responses, Applicants respectfully request that the rejections under 35 U.S.C. § 112, Second Paragraph, under 35 U.S.C. § 102, and under 35 U.S.C. § 103, be reconsidered and withdrawn. Applicants invite the Examiner to contact the undersigned Attorney to discuss any remaining issues with this application.

Applicants believe that the claims are in condition for allowance. Early favorable action is respectfully solicited.

Respectfully submitted,



Randall D. Morin
Attorney for Applicant(s)
Goodwin | Procter LLP
Exchange Place
53 State Street
Boston, Massachusetts 02109

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Reg. No. 58,312

Tel. No.: (617) 570-1657
Fax No.: (617) 523-1231